APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances by determining an appropriate point-of departure (i.e., no-observed-adverse-effect level or a benchmark dose) and then applying uncertainty factors. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vinyl Chloride
CAS Number: 75-01-4
Date: September 12, 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 28
Species: Rat

Minimal Risk Level: 0.5 [ ] mg/kg/day [X] ppm

References:

John JA, Smith FA, Leong BKJ, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39:497-513.

John JA, Smith FA, Schwetz BA. 1981. Vinyl chloride: Inhalation teratology study in mice, rats, and rabbits. Environ Health Perspect 41:171-177.

Experimental design: CF-1 mice were exposed to vinyl chloride at concentrations of 0, 50, or 500 ppm for 7 hours/day on gestational days 6–15 (John et al. 1977, 1981). Concurrent control groups were used, one for each dose level. Control groups were sham-exposed to filtered room air. Exposure was conducted in chambers of 3.7 m^3 volume under dynamic conditions. Animals were observed daily for clinical signs, and maternal body weights were determined several times during gestation. Animals were euthanized on gestational day 18 by carbon dioxide inhalation. Maternal liver weight was determined and uterine horns were examined. Fetuses were weighed, measured (crown-rump length), sexed, and subjected to gross and histopathological examinations.

Effects noted in study and corresponding doses: No adverse maternal or fetal effects were noted at 50 ppm, with the exception of a slight increase ($p<0.05$) in crown-rump length that was not observed at 500 ppm. The 50-ppm exposure level is considered to be a NOAEL for maternal and developmental toxicity. At the LOAEL of 500 ppm, delayed ossification ($p<0.05$) was observed. An increase in resorptions at 500 ppm was considered to have been within historical control limits. Significant changes in percentage resorption, litter size, and fetal body weight would not have been observed at 500 ppm if comparison had been made to the other control group. There was frank maternal toxicity at 500 ppm (17% death). The limited number and spacing of dose group precludes the use of benchmark dose modeling for determination of the point-of-departure for the MRL.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL [ ] benchmark dose

Uncertainty Factors used in MRL derivation:

- [ ] 10 for use of a LOAEL
- [X] 3 for extrapolation from animals to humans with dosimetric adjustment
- [X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.

If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: The intermittent exposure duration of 7 hours/day was duration-adjusted to continuous exposure according to the following equation:

Duration-adjusted NOAEL = NOAEL (50 ppm) x 7 hours/24 hours per day = 15 ppm.

Following EPA (1994g) methodology, the human equivalent concentration ($NOAEL_{HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / H_{b/g})_H]$. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal NOAEL is equivalent to the $NOAEL_{HEC}$. A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $NOAEL_{HEC}$.

The acute-duration inhalation MRL = duration-adjusted $NOAEL_{HEC}$ (15 ppm) ÷ 30 (UF) = 0.5 ppm.

Other additional studies or pertinent information which lend support to this MRL: Delayed ossification (500 ppm, the lowest concentration tested) was the only developmental effect observed in a rabbit developmental study (John et al. 1977/ 1981).

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vinyl Chloride
CAS Number: 75-01-4
Date: September 12, 2004
Profile Status: Final Pre-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: 0.03 [ ] mg/kg/day [X] ppm

Reference: Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68:207-219.

Experimental design: Groups of male and female Sprague-Dawley rats (30/sex/group) were exposed to vinyl chloride vapor concentrations of 0, 10, 100, or 1,100 ppm, 6 hours/day for 10 weeks prior to mating and during a 3-week mating period. F_0 males were exposed during the gestational period and sacrificed following the completion of parturition. F_0 females were exposed during gestation and lactation (with the exception of a break in exposure from gestation day 21 through postnatal day 4 to allow for delivery of litters). All F_0 rats were observed twice daily for clinical signs. Body weights and food consumption were monitored. F_1 litters were examined for live and dead pups and on lactation day 4, litters were culled to eight pups (equal numbers of male and female pups where possible). All F_0 female rats (including those that did not produce offspring) were sacrificed after the F_1 rats had been weaned. Reproductive tissues, adrenal glands, brain, kidneys, liver, lungs, spleen, thymus, mammary glands, nasal tissues, pituitary, and trachea from each of the F_0 rats were individually weighed and subjected to histopathologic examinations. At weaning, 15 male and female F_1 rats/group were selected for gross and microscopic examinations. Other F_1 rats were randomly selected to form groups of 30/sex/group, and these F_1 rats were subjected to the same treatment as the F_0 rats during the production of an F_2 generation. At weaning, 15 male and female F_2 rats/group were subjected to gross and microscopic examinations. Sperm parameters were assessed in 15 F_0 and 15 F_1 male rats of each exposure group.

Effects noted in study and corresponding doses: Absolute and relative mean liver weights were significantly increased at all exposure levels in F_0 males and in 100- and 1,100-ppm F_1 males. Slight centrilobular hypertrophy, considered to be a minimal adverse effect, was noted in the livers of all 1,100-ppm male and female F_0 and F_1 rats, most 100-ppm male and female F_0 and F_1 rats, and in 2/30 and 6/30 of the 10-ppm F_0 and F_1 female rats, respectively (see Table A-1). No incidences of centrilobular hypertrophy were found in any of the control rats. Compared to an incidence of 0/30 for this lesion in controls, the incidence of 6/30 in the 10-ppm F_1 female rats exceeded the level of statistical significance ($p<0.05$ according to Fisher's Exact Test performed by ATSDR).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] LEC_{10} from benchmark dose modeling

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
The incidence data for centrilobular hypertrophy in the male and female F_0 and F_1 rats exposed to vinyl chloride by inhalation, 6 hours/day for 10 weeks prior to mating and during mating, gestation, and lactation (Thornton et al. 2002) are shown in Table A-1.

Table A-1. Incidences of F_0 And F_1 Male and Female With Centrilobular Hypertrophy in the Liver Following Inhalation Exposure to Vinyl Chloride Vapors for 6 Hours/Day for 10 Weeks Prior to Mating and During Mating and Gestation (Males and Females) and Lactation (Females)

	Exposure concentration (ppm)			
	0	10	100	1,100
F_0 males	0/30	0/30	15/30*	30/30*
F_0 females	0/30	2/30	26/30*	30/30*
F_1 males	0/30	0/30	19/30*	30/30*
F_1 females	0/30	6/30*	30/30*	30/30*

*Statistically significantly ($p<0.05$) different from controls according to Fisher's Exact Test performed by ATSDR.

Source: Thornton et al. (2002)

All dichotomous models in the Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for centrilobular hypertrophy in the liver of the F_1 female rats, which had also been exposed via their mothers during pre- and post-natal development. The lower 95% confidence limit (LEC_{10}) of a 10% extra risk (EC_{10}) for hepatic centrilobular hypertrophy was selected as the benchmark response for the point of departure. The Quantal Quadratic model provided the best fit as assessed by a chi-square goodness-of-fit test and the Aikake's Information Criteria (AIC) (Table A-2). Therefore, the LEC_{10} value of 5 ppm, derived from the Quantal Quadratic model, was selected as the point of departure for calculating an intermediate-duration inhalation MRL (see Table A-2 and Figure A-1).

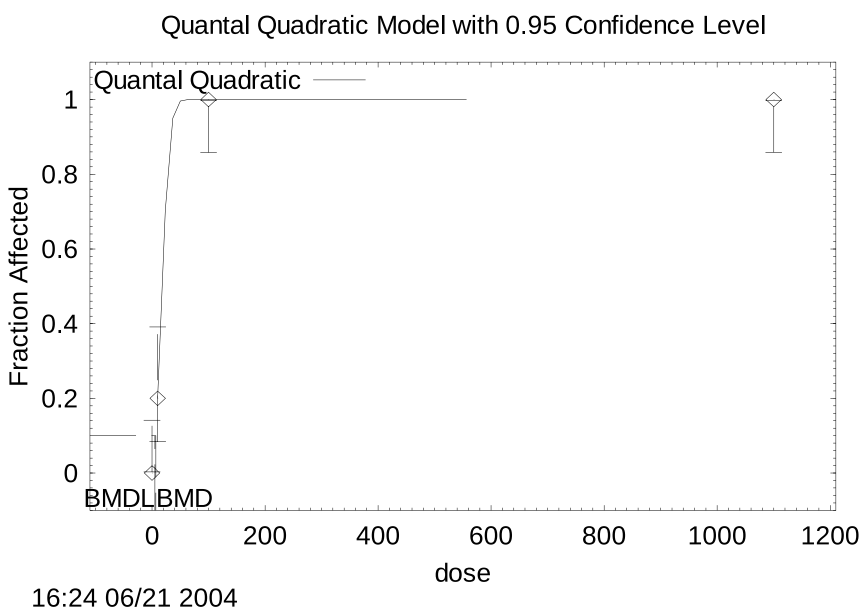
Table A-2. Modeling Results for the Incidence of F_1 Female Rats with Centrilobular Hypertrophy in the Liver Following Inhalation Exposure to Vinyl Chloride Vapors for 6 Hours/Day for 10 Weeks Prior to Mating and During Mating, Gestation, and Lactation, and Exposed via their Mothers During Pre- and Postnatal Development

Model	EC_{10} (ppm)	LEC_{10} (ppm)	χ^2 p-value	AIC
Gamma[a]	7.78	3.15	1.00	34.02
Logistic	8.75	6.15	1.00	32.05
Log-logistic[b]	9.12	5.22	1.00	34.02
Multi-stage[c]	6.35	3.44	undefined	36.02
Probit	9.11	5.69	1.00	34.02
Log-probit[b]	8.56	5.09	1.00	34.02
Quantal linear	3.03	2.05	0.53	35.28
Quantal quadratic	**6.87**	**5.08**	**1.00**	**32.02**
Weibull[a]	6.68	3.03	1.00	34.02

[a]Restrict power >=1
[b]Slope restricted to >1
[c]Restrict betas >=0; Degree of polynomial=3

Source: Thornton et al. 2002

Figure A-1. Benchmark Dose Model Results for the Incidence of Female F1 Rats with Centrilobular Hypertrophy Following Exposure to Vinyl Chloride by Inhalation, 6 Hours/Day for 10 Weeks Prior to Mating and During Mating, Gestation, and Lactation, and Exposed Via their Mothers During Pre- and Postnatal Development



The intermittent exposure duration of 6 hours/day was duration-adjusted to continuous exposure according to the following equation:

Duration-adjusted LEC_{10} = LEC_{10} (5 ppm) x 6 hours/24 hours per day = 1.25 ppm; (rounded to 1.0 ppm).

Following EPA (1994g) methodology, the human equivalent concentration (LEC_{10HEC}) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal LEC_{10} by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / (H_{b/g})_H]$. Since the partition coefficient in mice is greater than that in humans, as seen in Table 3-3, a default value of 1 is used for the ratio and the duration-adjusted animal LEC_{10} is equivalent to the LEC_{10HEC}. Several physiologically-based pharmacokinetic (PBPK) models are available for vinyl chloride; however, none of these models included an evaluation of exposure during mating, gestation, or lactation. Therefore, PBPK models could not be used to calculate a LEC_{10HEC} from the Thornton et al. (2002) study. A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $NOAEL_{HEC}$.

The intermediate-duration inhalation MRL = LEC_{10HEC} (1.0 ppm) ÷ 30 = 0.03 ppm.

<u>Other additional studies or pertinent information which lend support to this MRL</u>: Liver enlargement and/or histopathological changes have been noted in a number of intermediate-duration inhalation studies in animals (Bi et al. 1985; Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). The studies by Thornton et al. (2002) and Bi et al. (1985) show these effects at a somewhat lower dosage. Additional support comes from a study citing immunostimulation in mice at 10 ppm (Sharma and Gehring 1979).

<u>Agency Contact (Chemical Manager)</u>: G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Vinyl Chloride
CAS Number:	75-01-4
Date:	September 12, 2004
Profile Status:	Final Pre-Public Comment
Route:	[ ] Inhalation [X] Oral
Duration:	[ ] Acute [ ] Intermediate [X] Chronic
Graph Key:	5
Species:	Rat

Minimal Risk Level: 0.003 [X] mg/kg/day [ ] ppm

References:

Til HP, Immel HR, Feron VJ. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes, TNO. Report No. V 93.285/291099.

Til HP, Feron VJ, Immel HR. 1991. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.

Experimental design: Groups of Wistar rats (100/sex/group in controls and the two lowest exposure groups; 50/sex at the highest exposure level) were administered vinyl chloride in the daily diet at intended initial dietary concentrations of 0, 0.46, 4.6, or 46 ppm for 149 weeks. Due to rapid evaporative loss of vinyl chloride from the food, liquid vinyl chloride was mixed with polyvinyl chloride granules to produce a mixture in which vinyl chloride was effectively encapsulated in polyvinyl chloride granules (Feron et al. 1975). The study authors trained the rats to a feeding schedule of 4 hours/day prior to the initiation of exposure to vinyl chloride in the diet. The authors noted that food consumption per hour was fairly constant during the 4-hour feeding period. Loss of vinyl chloride from food during the first hour, the second hour, and the final 2 hours was calculated. Periodic food intake measurements were made for the first hour, the second hour, and the final 2 hours. Based on these measurements, the study authors calculated the average oral intake of the combined sexes during the daily 4-hour feeding periods to be 0, 0.018, 0.17, and 1.7 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively (see Table A-3). Measurements of vinyl chloride in the feces were made periodically at 1 hour prior to the feeding period, the end of the 4-hour feeding period, and 4 and 9 hours later. The study authors considered the vinyl chloride content in the feces to have remained encapsulated in the polyvinyl chloride granules and thus not to have been available for absorption from the gastrointestinal tract. The amount of vinyl chloride in the feces was subtracted from the calculated daily oral intake of vinyl chloride to arrive at what the study authors termed “actual oral exposure levels” of 0, 0.014, 0.13, and 1.3 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively (see Table A-3). Results of toxicokinetic assessments for vinyl chloride indicate that, following absorption, vinyl chloride and its metabolites are not excreted in appreciable amounts in the feces. Types and incidences of neoplastic and nonneoplastic liver lesions were determined at the end of the study.

Table A-3. Exposure Levels and Oral Intake Values for Rats Exposed to Vinyl Chloride in the Diet for 149 Weeks

Mean initial dietary level (ppm)	Oral intake (mg/kg/day)[a]	Adjusted oral intake (mg/kg/day)[b]	Estimated absorbed dose (mg/kg/day)[c]
0	0	0	0
0.49	0.022	0.018	0.014
4.49	0.21	0.17	0.13
44.1	2.1	1.7	1.3

[a]Assuming no loss of vinyl chloride by evaporation from the diet.
[b]Oral intake, adjusted for evaporative loss from the diet during the daily 4-hour feeding periods.
[c]Oral intake of vinyl chloride (adjusted for evaporative loss and the amount excreted in the feces, which was considered to have remained encapsulated in the polyvinyl chloride granules and not to have been available for absorption).

Source: Til et al. (1983, 1991)

Effects noted in study and corresponding doses: The critical nonneoplastic effect was determined to be liver cell polymorphism, which was classified by severity (slight, moderate, severe). The incidences of this lesion are listed in Table A-4.

Table A-4. Incidences of Male and Female Wistar Rats Exhibiting Slight, Moderate, or Severe Liver Cell Polymorphism Following Daily Oral Exposure to Vinyl Chloride in the Diet for 149 Weeks

	Oral intake (mg/kg/day)							
	Males				Females			
	0	0.018	0.17	1.7	0	0.018	0.17	1.7
Number of rats examined	99	99	99	49	98	100	96	49
Slight	27	23	26	19	46	41	49	23
Moderate	4	4	7	10[a]	14	13	8	15[b]
Severe	1	1	1	3	2	3	4	9[c]

[a]Significantly different from controls according to Fisher's exact test ($p<0.001$).
[b]Significantly different from controls according to Fisher's exact test ($p<0.05$).
[c]Significantly different from controls according to Fisher's exact test ($p<0.0001$).

Source: (Til et al. 1983, 1991)

A LOAEL of 1.7 mg/kg/day was identified for statistically significantly increased incidences of liver cell polymorphism in male and female rats. The NOAEL for nonneoplastic liver effects is 0.17 mg/kg/day. An increase in the incidence of female rats with many hepatic cysts was also observed at the highest dose (1.7 mg/kg/day). Other histopathologic lesions, described as hepatic foci of cellular alteration, were observed at all dose levels in female rats and in high-dose male rats, but were not used to derive an MRL because they are considered to be preneoplastic lesions. MRLs are protective only for non-neoplastic effects and do not reflect cancer risk.

The liver cell polymorphism incidences reported by Til et al. (1983, 1991) were also used as the basis of the RfD of 0.003 mg/kg/day for vinyl chloride derived by the U.S. EPA (EPA 2000). However, EPA used the estimated absorbed dose of 0.13 mg/kg/day as the NOAEL, rather than the adjusted oral intake NOAEL of 0.17 mg/kg/day used by ATSDR. EPA (2000) applied the Clewell et al. (1995) PBPK model for vinyl chloride to the low-, mid-, and high-dose groups (estimated absorbed doses of 0.014, 0.13, and 1.3 mg/kg/day, respectively) to generate dose metrics of 0.3, 3, and 30 mg vinyl chloride metabolites/L liver, respectively. The EPA (2000) rationale for using the total amount of metabolite generated divided by the volume of liver tissue as the dose metric for liver toxicity included evidence that vinyl chloride-induced liver toxicity is related to the production of reactive intermediates and that binding to liver macromolecules correlates well with total metabolism (Watanabe et al. 1978). In EPA's derivation of the RfD, it was assumed that all of the metabolism of vinyl chloride occurred in the liver. EPA (2000) simulated a continuous human exposure scenario (ingestion of 1 ppm of vinyl chloride in water or 0.286 mg/kg/day, assuming consumption of 2 L water/day for a 70-kg person) using the Clewell et al. (1995) model, which resulted in a human internal dose metric of 1.01 mg metabolite/L liver. The ratio of the value for the human internal dose metric 1.01 mg metabolite/L liver) to the vinyl chloride intake of 0.286 mg/kg/day in the simulated human exposure scenario (1.01 ÷ 0.286 = 35.31) was used by EPA (2000) to convert from the rat dose metric (3 mg metabolite/L liver) at the NOAEL (0.13 mg/kg/day estimated absorbed dose) to a human equivalent dose (i.e., the rat NOAEL of 0.13 mg/kg/day divided by 35.31 equals a human equivalent dose of 0.09 mg/kg/day). EPA considered this approach to be adequate because vinyl chloride metabolism is linear in the dose range that includes the NOAEL of 0.13 mg/kg/day identified in the rat study of Til et al. (1983, 1991).

EPA (2000) assessed the feasibility of using Benchmark Dose Modeling on incidence data for liver cell polymorphism in the study of Til et al. (1983, 1991). Incidence data for moderate and severe grades of liver cell polymorphism were combined for both sexes and summed to produce one control group and three exposure groups (moderate + severe incidences of liver cell polymorphism divided by the number of treated male and female rats at each dose level; 21/197 controls, 21/199 low-dose, 20/196 mid-dose, and 37/98 high-dose rats). The resulting incidence data for each dose metric (0.3, 3, and 30 mg metabolite/L liver) were subjected to Benchmark Dose modeling in order to statistically identify a threshold response for vinyl chloride-induced effects. The resulting dose metric values are shown in Table A-5.

Table A-5. LED_{10} Values Generated from Various Models to Liver Cell Polymorphism Incidence Data from Oral Exposure of Male and Female Rats to Vinyl Chloride in the Diet for 149 Weeks in the Study of Til et al. 1991

Model	LED_{10} (mg/L liver)[a]	*p*-value
Weibull (power≥1)	24.0	0.88
Gammahit	21.4	0.88
Quantal quadratic	13.8	0.96
Logistic	12.9	0.47
Multistage	11.8	0.79
Probit	11.6	0.44
Quantal linear	6.5	0.46
NOAEL	3.00 (0.13 mg/kg/day)	
LOAEL	29.9 (1.3 mg/kg/day)	

[a]LED_{10} is the lower 95% confidence limit of a 10% change in numbers exhibiting polymorphism evaluated as either moderate or severe. The NOAEL and LOAEL are shown for comparison.

Source: EPA (2000)

EPA (2000) noted that although all models provided adequate fit to the data, the liver cell polymorphism appeared to be only a high-dose phenomenon, the LED_{10} values ranged from 6.5 to 24.01 mg/L liver (nearly a 4-fold range), and all modeled LED_{10} values were higher than the NOAEL of the study. EPA (2000) argued that there was no biological reason to choose the results of one model over another and that the dose-response characteristics present additional uncertainty due to the large gaps between dose levels. For these reasons, EPA (2000) chose to use the internal dose metric of 3 mg/L liver, corresponding to the rat NOAEL, rather than a benchmark LED_{10} value, to derive the RfD for vinyl chloride. EPA (2000) applied an uncertainty factor of 30 (3 for extrapolating from animals to humans using a dosimetric adjustment and 10 for intrahuman variability) to the HED of 0.09 mg/kg/day.

Therefore, the RfD = 0.09 mg/kg/day ÷ 30 = 0.003 mg/kg/day. The chronic-duration oral MRL for vinyl chloride is based on the same critical effect as that used by EPA (2000) to derive the RfD for vinyl chloride (i.e., the NOAEL for liver cell polymorphism in the oral rat study of Til et al. 1983, 1991). However, the point of departure for the chronic-duration oral MRL was the NOAEL of 0.17 mg/kg/day (average ingested dose), rather than the estimated absorbed dose of 0.13 mg/kg/day used by EPA (2000), based on the assumption that all of the vinyl chloride that remained in the diet (after volatilization) was available for absorption.

In deriving the MRL, the rat NOAEL of 0.17 mg/kg/day was converted to a human equivalent dose using the PBPK models described in Clewell et al. (2001) and EPA (2000) to extrapolate from rats to humans. Source code and parameter values for running the rat and human models in Advance Continuous Simulation Language (ACSL) were transcribed from Appendix C of EPA (2000). Parameter values used in the interspecies extrapolation are presented in Table A-6. Accuracy of the implementation of the model in ACSL (v. 11.8.4) was checked against observations reported in Gehring et al. (1978), also reported in Clewell et al. (2001) (results shown in Figure A-2). The total amount of vinyl chloride metabolized in 24 hours per L of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures, for which, the average daily dose was equivalent to the NOAEL dose for liver effects (ADD, 0.17 mg/kg/day). This dose was uniformly distributed over a 4-hour period (i.e., 0.0425 mg/kg/hour for 4 hours, followed by 16 hours at 0 mg/kg/hour). Dose metrics reflect the cumulative amount of vinyl chloride metabolized over the 24-hour period.

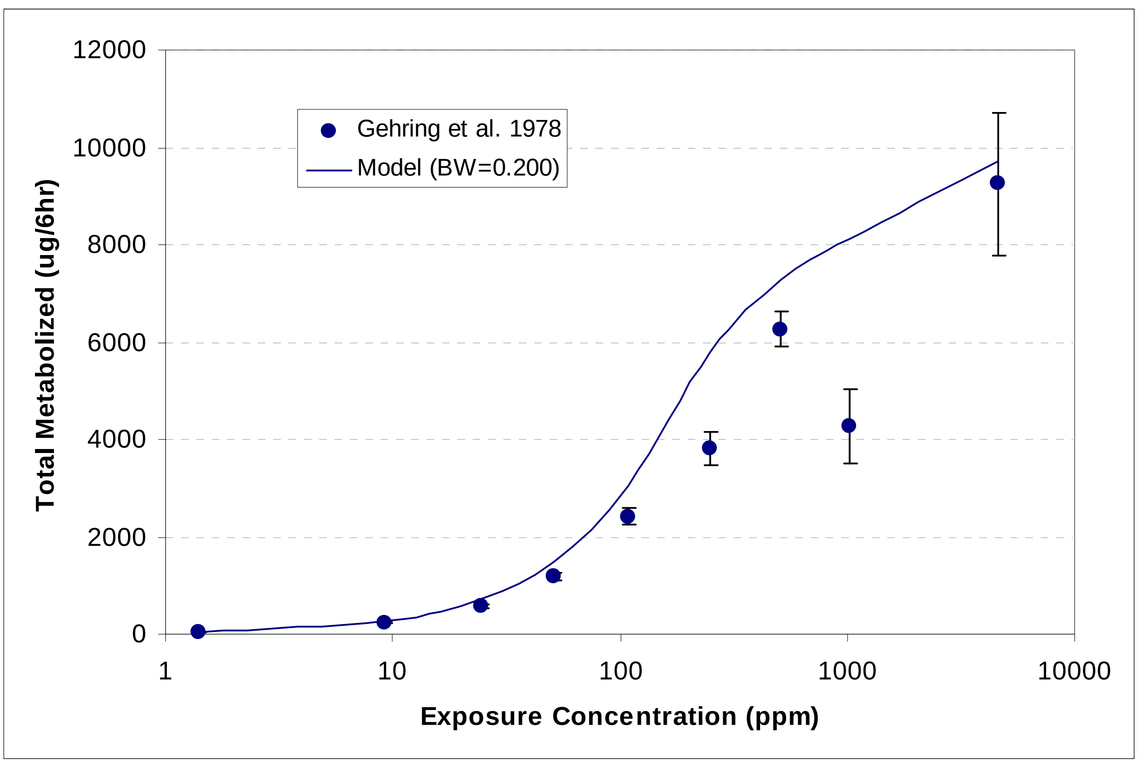
Table A-6. Parameter Values for Rat and Human Models

		Model	
Parameter	Definition	Rat	Human
BW	Body weight (kg)	0.377 (m) 0.204 (f)	70
VLC	Liver volume (fraction of body)	0.05	0.026
VFC	Fat volume (fraction of body)	0.12	0.19
VSC	Slowly-perfused tissue volume (fraction of body)	0.75	0.63
VRC	Rapidly-perfused tissue volume (fraction of body)	0.05	0.064
QCC	Cardiac output (L/hr-kg body weight)	18.0	16.5
QPC	Alveolar ventilation rate (L/hr-kg body weight)	21.0	24.0
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.26
QFC	Fat blood flow (fraction of cardiac output)	0.09	0.05
QSC	Slowly-perfused blood flow (fraction of cardiac output)	0.15	0.19
QRC	Rapidly-perfused blood flow (fraction of cardiac output)	0.51	0.5
PB	Blood:air partition coefficient	2.4	1.16
PL	Liver:blood partition coefficient	0.7	1.45
PF	Fat:blood partition coefficient	10.0	20.7
PS	Slowly-perfused partition coefficient	4.0	0.83
PR	Rapidly-perfused partition coefficient	0.7	1.45

Table A-6. Parameter Values for Rat and Human Models

Parameter	Definition	Model Rat	Model Human
VMAX1C	Maximum rate of oxidative metabolism (mg/hr-kg body weight)	4.0	4.0
VMAX2C	Maximum rate of oxidative metabolism (mg/hour-kg body weight)	2.0	0.1
KM1	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	0.1	0.1
KM2	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	10.0	10.0
KCO2C	Rate constant for formation of CO_2 from oxidative metabolite ($hour^{-1}$)	1.6	1.6
KGSMC	Rate constant for conjugation with GSH ($hour^{-1}$)	0.13	0.13
KFEEC	Rate constant for conjugation, not with GSH ($hour^{-1}$)	35.0	35.0
CGSZ	Initial GSH concentration in liver (µmol/L)	5,800	5,800
KBC	Rate constant for GSH catabolism ($hour^{-1}$)	0.12	0.12
KS	Coefficient controlling resynthesis of GSH (µmol/L)	2,000	2,000
KZC	Zero-order rate constant for resynthesis of GSH (µmol/hour)	28.5	28.5
Ka	Gastrointestinal absorption rate constant ($hour^{-1}$)	3.0	

Figure A-2. Predicted and Observed Relationship Between Air Exposure Concentration and Rate Metabolism of Vinyl Chloride in Rats*



*Measurements of metabolites (non-volatile ^{14}C in carcass) were made immediately following a 6-hour exposure to [^{14}C]vinyl chloride in air. Circles represent observations (± SD); the line shows the corresponding simulations.

The human model was run iteratively, varying the ADD, until the model converged with the internal dose estimate shown in row 1 in Table A-7 (rat, male). The value for the Km1 for oxidative metabolism in humans was assumed to be equal to the Km1 value for rats (0.1 mg/L) (EPA 2000). The human ADD was assumed to be uniformly distributed over a 24-hour period. The resulting HED was 0.09 mg/kg/day (see Table A-7). Additional simulations were performed assuming that the ADD was distributed over a 12-hour period (to simulate exposure from drinking water or food during the day only). The resulting dose metrics were very similar to the 24-hour estimates (data not shown).

Table A-7. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses

Species	BW (kg)	Km1 mg/L	ED (week)	EF1 (day/ week)	EF2 (hour/ day)	ADD (mg/kg/day)	DM (mg/L)
Wistar rat							
Male	0.377	0.1	149	7	4	0.17	3.16
Female	0.204	0.1	149	7	4	0.17	3.16
Human	70	0.1	3,640	7	24	0.09	3.16

ADD = average daily administered dose; BW = body weight; DM = dose metric equals the total amount of metabolite formed in 24 hours per L of liver; ED = exposure duration; EF = exposure frequency; Km1 = Michaelis-Menten constant for oxidative metabolism

ATSDR accepted the rationale used by EPA (2000) for not using Benchmark Dose modeling results for incidences of the critical effect (liver cell polymorphism in the oral rat study of Til et al. 1983, 1991) in the risk assessment. Therefore, the HED of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied to the HED.

Therefore, the chronic-duration oral MRL = 0.09 mg/kg/day (HED) ÷ 30 = 0.003 mg/kg/day.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans using a dose metric conversion
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
N/A

Other additional studies or pertinent information which lend support to this MRL: This MRL is reinforced by a study by Feron et al. (1981) in which rats were fed diets containing PVC powder.

Increased areas of cellular alteration (consisting of clear foci, basophilic foci, and eosinophilic foci) were observed in the liver of rats at an oral intake of vinyl chloride monomer of 1.8 mg/kg/day.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

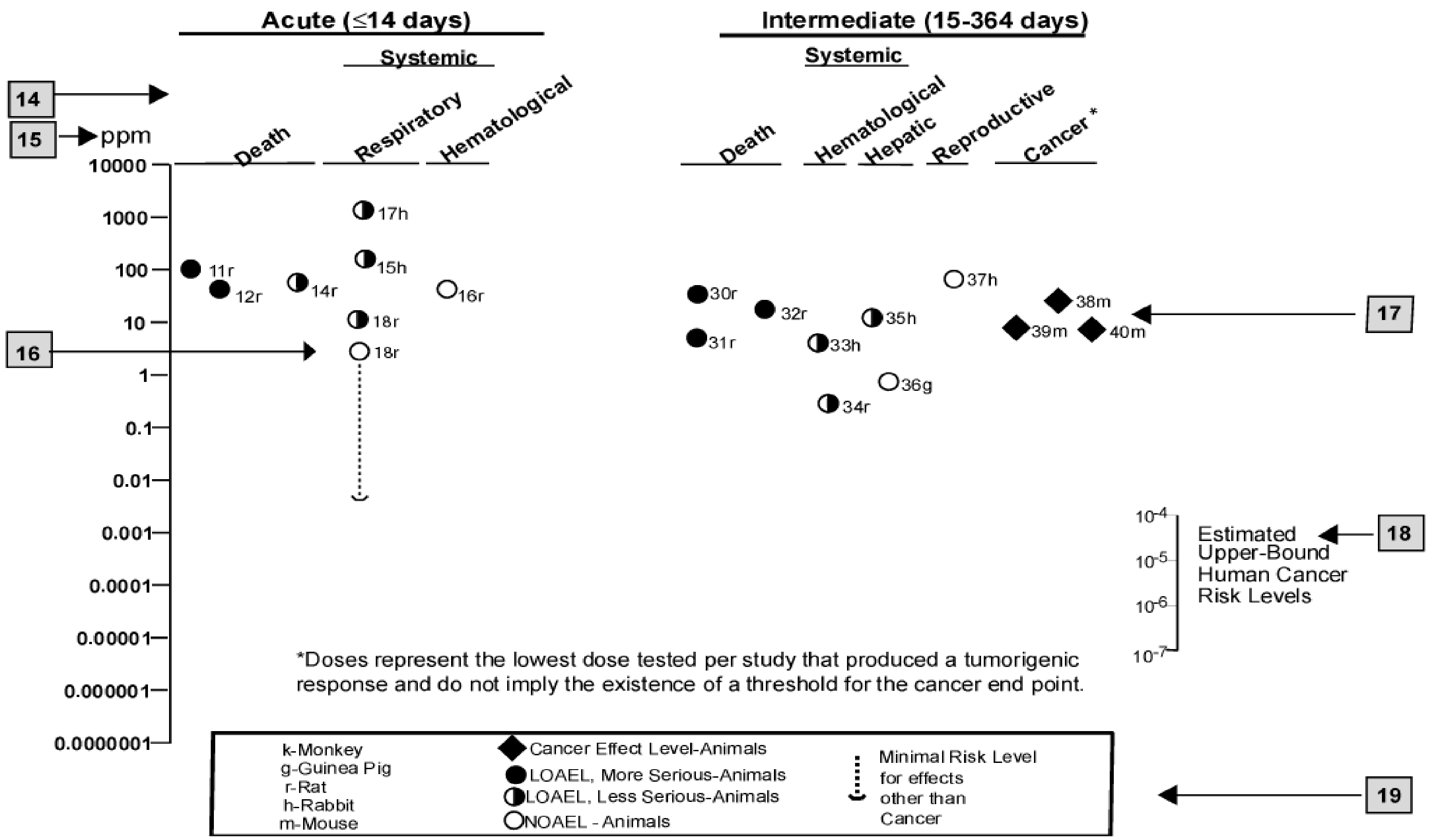
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
3 →	Systemic							
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer						11 ↓	
	38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
	39	Rat	89-104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



DRAFT FOR PUBLIC COMMENT

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D. INDEX